BREXIPIPRAZOLE (**REXULTI)**

## Pharmacology

### Mechanism of Action

Serotonin-dopamine activity modulator (SDAM) that acts as a partial agonist at 5-HT1A and dopamine D2 receptors at similar potency, and an antagonist at 5-HT2A and noradrenaline alpha1B/2C receptors

### Absorption

Absolute bioavailability: 95%

Peak plasma time: 4 hr

Steady-state concentration: 1-12 days

### Distribution

Protein bound: >99% to serum albumin and alpha-1-acid glycoprotein; its protein binding is not affected by renal or hepatic impairment

Brexpiprazole protein binding is not affected by warfarin, diazepam, or digitoxin

Vd: 1.56 L/kg

### Metabolism

Metabolized primarily by CYP2D6 and CYP3A4 isoenzymes

### Elimination

Half-life: 91 hr

Clearance: 19.8 mL·hr/kg

Excretion: 25% urine; 46% feces

Partial agonist at D2

High affinity for Ser 5-HT1a partial agonist

5-HT2a, alpha 1b , and 2c - adrenoceptors antagonism

2 and 4 mg.

inc prolactin

akathesia

weight gain

no effect on cardiac conduction

**Schizophrenia**

Indicated for schizophrenia

Recommended starting dose: 1 mg PO qDay on Days 1 through 4

Recommended target dose: 2-4 mg PO qDay; titrate to 2 mg qDay on Days 5 through 7, and then to 4 mg/day on Day 8 based on the patient’s clinical response and tolerability

Not to exceed 4 mg/day

Periodically reassess to determine the continued need and appropriate dose

**Depression**

Indicated as adjunctive treatment for major depressive disorder

Recommended starting dose: 0.5 mg or 1 mg PO qDay

Recommended target dose: 2 mg PO qDay; at weekly intervals, titrate to 1 mg/day, and then up to 2 mg/day

Titrate according to clinical response and tolerability

Not to exceed 3 mg/day

Periodically reassess to determine the continued need and appropriate dose

Used as an adjuvant to treat depression.

**Dosage Forms & Strengths**

tablet

* 0.25mg
* 0.5mg
* 1mg
* 2mg
* 3mg
* 4mg

**Dosage Modifications**

Hepatic impairment

* Moderate-to-severe hepatic impairment (Child-Pugh ≥7)
	+ MDD: Not to exceed 2 mg/day
	+ Schizophrenia: Not to exceed 3 mg/day

Renal impairment

* Moderate, severe, or ESRD (CrCl <60 mL/min)
	+ MDD: Not to exceed 2 mg/day
	+ Schizophrenia: Not to exceed 3 mg/day

CYP2D6 poor metabolizers

* CYP2D6 poor metabolizers: Administer half of the usual brexpiprazole dose
* Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors: Administer a quarter of the usual brexpiprazole dose

CYP2D6 or CYP3A4 inhibitors

* Strong CYP2D6 inhibitors: Administer half of the usual brexpiprazole dose (see note below for MDD)
* Strong CYP3A4 inhibitors: Administer half of the usual brexpiprazole dose
* Strong/moderate CYP2D6 inhibitors plus strong/moderate CYP3A4 inhibitors: Administer a quarter of the usual brexpiprazole dose
* If the coadministered drug is discontinued, adjust the brexpiprazole dosage to its original level
* NOTE: In MDD clinical trials, brexpiprazole dosage was not adjusted for strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine); thus, CYP considerations are already factored into general dosing recommendations and brexpiprazole may be administered without dosage adjustment in patients with MDD

CYP3A4 inducers

* Strong CYP3A4 inducers: Double usual dose over 1 to 2 weeks
* If the coadministered CYP3A4 inducer is discontinued, reduce the brexpiprazole dosage to the original level over 1-2 weeks

**Geriatric Dosage & Uses**

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis

Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis (see Black Box Warnings)

#### Serious - Use Alternative (1)

* Nelfinavir

## Adverse Effects

### >10%

Akathisia (4-14%)

### 1-10%

Headache (4-9%)

Weight increased (3-8%)

Nasopharyngitis (1-7%)

Extrapyramidal symptoms, excluding akathisia (5-6%)

Somnolence (4-6%)

Dyspepsia (2-6%)

Constipation (1-6%)

Tremor (2-5%)

Fatigue/sedation (2-5%)

Dizziness (1-5%)

Increased CPK blood levels (2-4%)

Decreased cortisol levels (2-4%)

Anxiety (2-4%)

Restlessness (2-4%)

Increased appetite (2-3%)

Diarrhea (1-3%)

### Frequency Unknown Dystonia

## Warnings

### Black Box Warnings

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death; brexpiprazole is not approved for the treatment of patients with dementia-related psychosis

Antidepressants increase the risk of suicidal thoughts and behaviors in patients aged ≤24 yr; monitor for clinical worsening and emergence of suicidal thoughts and behaviors

Safety and effectiveness have not been established in pediatric patients

### Contraindications

Hypersensitivity; reactions have included rash, facial swelling, urticaria, and angioedema

### Cautions

Increased mortality in elderly patients with dementia-related psychosis (see Black Box Warnings); in placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared with placebo

Suicidal thoughts and behaviors reported in children, adolescents, and young adults who are taking antidepressant drugs (see Black Box Warnings)

Potentially fatal neuroleptic malignant syndrome (NMS) reported in association with administration of antipsychotic drugs

Potentially irreversible, involuntary, dyskinetic movements (ie, tardive dyskinesia) reported with antipsychotic drugs; incidence highest in elderly persons, especially elderly women

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus (including extreme cases associated with ketoacidosis or hyperosmolar coma or death), dyslipidemia, and body weight gain

May cause leukopenia, neutropenia, and agranulocytosis; monitor and discontinue if severe neutropenia (ANC <1000/mm³)

Orthostatic hypotension or syncope may occur (rare)

Caution with a history of seizures or with conditions/drugs that potentially lower the seizure threshold

Body temperature dysregulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents

Dysphagia: Esophageal dysmotility and aspiration pneumonia reported

Sedation and hypersomnia reported that may cause impaired judgement, thinking, or motor skills

## Pregnancy

### Pregnancy

Rexulti pregnancy exposure registry: Monitors pregnancy outcomes in women exposed to brexpiprazole during pregnancy; for more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancy

Adequate and well-controlled studies have not been conducted with brexpiprazole in pregnant women to inform drug-associated risks; however, neonates whose mothers are exposed to antipsychotic drugs, like brexpiprazole, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms (eg, agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder)

Animal reproduction studies

* No teratogenicity was observed with oral administration of brexpiprazole to pregnant rats and rabbits during organogenesis at doses up to 73 and 146 times, respectively, of maximum recommended human dose (MRHD) of 4 mg/day on a mg/m² basis
* However, when pregnant rats were administered brexpiprazole during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 73 times the MRHD

### Lactation

Unknown if distributed in human breast milk

Present in rat milk

The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for the drug and any potential adverse effects on the breastfed infant from the drug or from the underlying maternal condition

### Pregnancy Categories

A:Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B:May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C:Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.

D:Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.

X:Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA:Information not available.